UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,177	08/13/2007	Andreas Ehlich	0066-0007-US1	5698

91436 7590 10/11/2011

Fanelli Haag PLLC
1909 K Street, N.W., Suite 1120
Washington, DC 20006

EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/11/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,177	EHLICH, ANDREAS	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,4,6-47,49-53 and 55* is/are pending in the application.

5a) Of the above claim(s) *10,13-47 and 49-53* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 4, 6-9, 11-12 and 55* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/27/2011 has been entered.

Applicant's response of 09/27/2011 to office action mailed on 03/30/2011 is entered.

Claims 1, 4 & 6 are amended.

Claim 55 is new

Claims 10, 13-47 and 49-53 are withdrawn

Claims 2, 3, 5, 48, and 54 are cancelled.

Claims 1, 4, 6-47, 49-53 and 55 are pending.

Claims 1, 4, 6-9, 11-12 and 55 are presently under examination.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Withdrawn Claim 1, 4, 6-9 and 11-12 rejections under 35 U.S.C. 112, second paragraph, for the reasons of record as set forth in the Office Action mailed on 03/30/2011 is withdrawn in view of Applicants amendments to the cited claims.

Withdrawn: 1, 4, 6-9 and 11-12 rejections under 35 U.S.C. 112, first paragraph (scope of enablement) for the reasons of record as set forth in the Office Action mailed on 03/30/2011 is withdrawn in view of Applicants amendments to the cited claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6-9, 11-12 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as there is no conclusion which is commensurate with the preamble. Hence, the determination of the amount or activity is not clear how it relates to the preamble. Still further, for embodiments where the "amount or activity" is not found, it is not clear how this can be utilized for monitoring differentiation, as no differentiation is had, apparently. Hence, it is not clear if the claim is complete, or requires more, perhaps from the specification.

Claims 4, 6-9, 11-12 and 55 are rejected for depending from a rejected base claim(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6-9, 11-12 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims broadly require a generic cell differentiation into at least a generic final cell type. A generic cell that is being differentiated contains at least one generic recombinant nucleic acid molecule comprising a generic reporter gene encoding a protein that is secreted. Invention further drawn to non-human transgenic animals comprising said generic cells and generic final cell types. The claims further broadly claim "conditions

allowing differentiation of said cells" in vitro or in live non-human animals. The generic claiming of "cells capable of differentiating into at least one particular cell type" is extremely broad. Applicant describes a Markush group of desired cell types to differentiate into, e.g., p. 18 of the specification as filed from the PCT on 9/25/06, paragraph 2 (Also found in Claim 7). Such group includes very large genera, and really no specific differentiated cell type. For example, "fibroblasts" is a cell type which is generic and not any particular differentiated cell type, the cells of the stroma are multiple cell types, and the hematopoietic cells include all blood, muscle, and bone marrow cells at the very minimum. Given the broad listings of cell types, which indicate any differentiation of any cell of any generic cell, and the lack of specific linking between the generic cell capable of differentiating, and what they can differentiate into, there is a lack of description of the generic "conditions allowing for differentiation of said cells" for the breadth of cells encompassed prior to and upon differentiation. Applicant broadly describes cell types envisioned for differentiation, description of ES and EG cells, and some random mentions of other cells can differentiate into other cell types, but the breadth of the generic cells of each time (prior to and upon differentiation) and only a teaching of retinoic acid with regard to a single cell type in the examples. Given such broad scope and breadth of instant claims the Artisan would not be able to envision Applicant to have possessed the conditions which allow differentiation of the cells types for their breadth.

The specification however, has not provided a sufficient number of embodiments of conditions for the generic breadth of stem cells and differentiated cells, to provide a description of the generic breadth of conditions. The specification clearly fails to describe a single embodiment of even a single stem cell type and particular final cell type, in a generic mammal. Further it fails to describe even one condition which will not allow for differentiation of a specific cell capable of differentiation in a generic animal.

Applicant is referred to the guidelines for *Written Description Requirement* published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. In analyzing whether the written description requirement is

met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics.

Since the specification fails to set forth even one specific embodiment which is encompassed by the claims, it is not possible to envision the broadly claimed cell types, non-human animals possessing said cell types and broadly claimed conditions of differentiation the Artisan would not have understood Applicant to have been in possession of the genera claimed at the time of invention. One cannot describe what one has not conceived. Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Accordingly one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of a single member of this genus would not be representative of claimed genus of compounds and is insufficient to support the claim in its present scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 6-9 and 11-12 stand rejected under 102(b) as being anticipated by Benkel et al (WO 98/49320).

The above claims are drawn to a method of monitoring cell differentiation comprising steps of culturing cells capable of differentiating wherein said cells contain at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation and at least one cell type-specific promoter sequence operably linked to said reporter gene or maintaining a non-human animal comprising said cells under conditions allowing differentiation and determining the amount of activity of the reporter gene product in the culture medium or in the body fluid and wherein said reporter gene product comprises a secretory leader sequence and the secreted reporter gene product is not recaptured from said body fluid or cell culture medium. In still further limitation the determining includes correlating the amount or activity of the secreted reporter gene product within a body fluid of said transgenic animal or the cell culture medium of said cells, with the amount of cells differentiated.

WO 98/49320 teaches the advantages of using a reporter gene system for studying the regulation of gene expression that is of fundamental importance among others to cell division and cell differentiation. Further towards this goal WO 98/49320 teaches reporter genes whose expression product is secretable for monitoring the same (entire article; abstract). WO 98/49320 teaches that there are several secretable reporter systems that including a secreted alkaline phsophatase (SEAP), alpha-amylase, hGH etc (p.1-2) and further exemplifies the use of a secretable alpha-amylase gene with a signal peptide coding region and tissue of cell type specific promoters and the measurement of the secreted product is simple, quantitative, sensitive safe, inexpensive and superior to other secretable reporters as the range of available variants of alpha-amylase allows the assays to be performed in virtually any host without any interference i.e., non-recaptured after secretion and fully available for assay (entire article; p.1-3; p.6-9). The cited art thus clearly anticipates the invention.

Applicants Arguments in the response of 09/27/2011:

The Applicant amends claims and argues that Benkel reference only describes a secreted reported system based on one or more amylases (p.15, 1st paragraph of Applicants response of 09/27/2011). The Applicant further argues it does not describe a method of monitoring cell differentiation and at most Benkel application has a single statement in the abstract about cell differentiation (p.15, 1st paragraph of Applicants response of 09/27/2011) and therefore, the applicant argues, the anticipation rejection is improper and should be withdrawn.

The Applicant arguments are however found, not persuasive because the Applicants base claim embraces all the reporter gene system including alpha-amylase as taught in Benkel. And specifically the dependent claim 9 for example (as well as the instant specification) emphasizes the use of alpha-amylase gene product as one of the preferred reporter for the instant invention. Hence the Applicants arguments regarding the same lack merit. Further the Applicants arguments regarding Benkel reference referring only once regarding usefulness of amylase reporters in monitoring differentiation also lacks merit because there is no requirement for an anticipatory reference to be repeat the same invention multiple times. Hence the rejection is proper and is being maintained as such with revisions as above to address the amendments to the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 6-9, 11-12 and 55 stand rejected under 35 USC 103 (a) as being unpatentable over Benkel et al (WO 98/49320; art of record) a in view of Goldspink et al., (US 2003/0008836 A1; art of record) and Bronstein et al., (1994, Biotechniques 17: 172-177; art of record)

The above claims are drawn to a method of monitoring cell differentiation comprising steps of culturing cells capable of differentiating wherein said cells contain at least one recombinant nucleic acid molecule comprising a reporter gene encoding a

product that is secreted upon cell differentiation and at least one cell type-specific promoter sequence operably linked to said reporter gene or maintaining a non-human animal comprising said cells under conditions allowing differentiation and determining the amount of activity of the reporter gene product in the culture medium or in the body fluid and wherein said reporter gene product comprises a secretory leader sequence and the secreted reporter gene product is not recaptured from said body fluid or cell culture medium. In still further limitation the determining includes correlating the amount or activity of the secreted reporter gene product within a body fluid of said transgenic animal or the cell culture medium of said cells, with the amount of cells differentiated.

Benkel (WO 98/49320) teaches the advantages of using a reporter gene system for studying the regulation of gene expression that is of fundamental importance among others to cell division and cell differentiation. Further towards this goal WO 98/49320 teaches reporter genes whose expression product is secretable for monitoring the same (entire article; abstract). WO 98/49320 teaches that there are several secretable reporter systems that including a secreted alkaline phsophatase (SEAP), alpha-amylase, hGH etc (p.1-2) and further exemplifies the use of a secretable alpha-amylase gene with a signal peptide coding region and tissue of cell type specific promoters and the measurement of the secreted product is simple, quantitative, sensitive safe, inexpensive and superior to other secretable reporters as the range of available variants of alpha-amylase allows the assays to be performed in virtually any host without any interference i.e., non recaptured after secretion and fully available for assay (entire article; p.1-3; p.6-9).

Regarding claims Goldspink clearly teaches a method of detecting myoblast differentiation by transfecting recombinant nucleic acid molecules encoding a human alpha-gal reporter gene under the control of promoter comprising MLC1/3 enhancer to undifferentiated myoblasts wherein the reporter gene was expressed and secreted from differentiated muscle cell in vitro culture (entire article; abstract; specifically paragraphs (0052-0059).

Bornstein teaches improvements in the detection sensitivity of SEAP reporter using chemiluminiscent assays of the secreted reporter from cells in culture or tissuse (entire article; abstract).

Thus it would have been obvious for one of ordinary skill in the art to incorporate SEAP reporter gene of Benkel for lacZ gene in the reporter construct of Goldspink and follow the differentiation of stem cells to specific tissue types or cell types using vry sensitive SEAP assays taught by Bornstein. One of ordinary skill in the art would have been motivated to make and use of an assayable secreted reporter that will not be captured by tissues or the cells for monitoring a gene regulation during differentiation of a cell into tissue cell type as it is less invasive and avoids lysis of the cells. One of ordinary skill in the art would have reasonable expectation of success making using recombinant progenitor or stem cell having a reporter gene construct that codes for a secretable reporter protein for evaluating and identifying the differentiated cells as the art teaches that it is routine to use a recombinant secretable reporter for marking differentiation. Thus, the claimed invention was *prima facie* obvious.

Applicants Arguments in the response of 09/27/2011:

The Applicant amends claims and argues that Benkel reference only describes a secreted reported system based on one or more amylases (p.15, 1st paragraph of Applicants response of 09/27/2011). The Applicant further argues it does not describe a method of monitoring cell differentiation and at most Benkel application has a single statement in the abstract about cell differentiation (p.15, 1st paragraph of Applicants response of 09/27/2011). Applicant further argues that Benkel teaches away from using SEAP as a reporter as Benkel teaches that amylase is superior to SEAP.

The Applicants arguments are however found, not persuasive because the Applicants base claim embraces all the reporter gene system including alpha-amylase as taught in Benkel. And specifically the dependent claim 9 for example (as well as the instant specification) emphasizes the use of alpha-amylase gene product as one of the preferred reporter for the instant invention. Hence the Applicants arguments regarding the same lack merit. Further the Applicants arguments regarding Benkel reference referring only once regarding usefulness of amylase reporters in monitoring differentiation also

lacks merit because there is no requirement for an anticipatory reference to be repeat the same invention multiple times. Applicants' further argument regarding Benkel reference teaching away from using SEAP as reporter is incorrect because the preferred use of amylase over SEAP does not mean teaching away from using SEAP. Further Applicant should note that the instant invention includes using alpha-amylase as one of the preferred reporters. Hence the rejection is proper and is being maintained as such with revisions as above to address the amendments to the claim. Applicants' further argument regarding Bornstein reference teaching away from using SEAP as reporter is incorrect because the superiority of several other reporter enzymes investigated by Bornstein over SEAP does not mean teaching away from using SEAP. Indeed Bornstein considers SEAP is one among the most sensitive reporters used in his assays (for example see abstract). Further Applicant should note that the instant invention broadly claims all the reporters in base claim and further includes using alpha-amylase as one of the preferred reporters in the dependent claims (for example claim 9). Unlike the Applicants arguments that the prior art only teaches assays of the reporter after a recapture from the medium (For example with reference to Goldspink) Bornstein clearly teaches assaying the SEAP directly in an aliquot of culture supernatant (see Bornstein p. 1544, col.1, 2nd paragraph). The Applicant further should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." Hence the rejection over obviousness of the invention over the prior art is proper and is being maintained as such with revisions as above to address the amendments to the claim.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.,* may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/ROBERT M KELLY/

Primary Examiner, Art Unit 1633